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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/724,953	11/28/2000	Dale B. Schenk	209-US-NEWS6	9560

20350 7590 07/25/2003

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EXAMINER
NICHOLS, CHRISTOPHER J

ART UNIT	PAPER NUMBER
1647	18

DATE MAILED: 07/25/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/724,953	SCHENK, DALE B.	
	Examiner	Art Unit	
	Christopher Nichols, Ph.D.	1647	

-- The MAILING DATE of this communication appears on th cover sheet with th correspond nc address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 May 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-11,14,16,18,19,21-25 and 58* is/are pending in the application.

4a) Of the above claim(s) *1-10* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *11,14,16,18,19,21-25 and 58* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *28 May 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *15* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Status of Application, Amendments, And/Or Claims

1. The Amendments filed 23 May 2003 (Paper No. 11) and 28 May 2003 (Paper No. 17) have been entered in full. Claims 11, 14, 16, 18, 19, and 21-25 have been amended. Claim 58 has been added. Claims 12, 13, 15, 17, 20, and 26-57 have been cancelled. Claims 1-10 remain withdrawn from consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected material, there being no allowable generic or linking claim. Claims 11, 14, 16, 18, 19, 21-25, and 58 are under examination.

2. The Applicant's continued traversal of the Restriction requirement as set forth in Office Action Paper No. 7 (26 March 2002) is noted and maintained for the reasons as set forth in the previous Office Action Paper No. 10 (27 November 2002).

3. Citations #144, #162, #174, and #186 have been taken into consideration.

4. The Applicant has requested that the double patenting rejections be held in abeyance until indication of allowability in the instant application. The Examiner *accepts* this and herein indicates whether or not the rejections under double patenting as set forth at pp. 11-14 ¶24-33 in the previous Office Action (Paper No. 10, 27 November 2002) have been *obviated* by amendment and if not, has maintained them where appropriate.

5. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Withdrawn Objections And/Or Rejections

6. The objection to the specification as set forth at pp. 4 ¶7-8 of the previous Office Action (Paper No. 10, 27 November 2002) is *withdrawn* in view of Applicant's amendments (Paper No. 17, 28 May 2003).

7. The objection to the drawings as set forth at pp. 5 ¶9 of the previous Office Action (Paper No. 10, 27 November 2002) is *withdrawn* in view of Applicant's amendments (Paper No. 17, 28 May 2003).

8. The objection to the claims as set forth at pp. 5 ¶10 of the previous Office Action (Paper No. 10, 27 November 2002) is *withdrawn* in view of Applicant's amendments (Paper No. 17, 28 May 2003).

9. The rejection of claims 11-25 under 35 U.S.C. §101 (double patenting) as set forth at pp. 11 ¶21 of the previous Office Action (Paper No. 10, 27 November 2002) is *withdrawn* in view of Applicant's amendments (Paper No. 17, 28 May 2003).

10. The rejection of claims 11-25 under 35 U.S.C. §112 ¶1 as set forth at pp. 5-10 ¶11-20 of the previous Office Action (Paper No. 10, 27 November 2002) is *withdrawn in part* in view of Applicant's amendments (Paper No. 17, 28 May 2003).

11. The rejection of claims 12, 13, 15, 17, and 20 under 35 U.S.C. §112 ¶1 as set forth at pp. 5-10 ¶11-20 of the previous Office Action (Paper No. 10, 27 November 2002) is *moot* in view of Applicant's cancellation of said claims (Paper No. 17, 28 May 2003).

12. The rejection of claims 11 and 16 under 35 U.S.C. §102(e) as set forth at pp. 14 ¶30 in the previous Office Action (Paper No. 10, 27 November 2002) is *withdrawn* in view of Applicant's amendments (Paper No. 17, 28 May 2003).

Maintained Objections And/Or Rejections

13. Claims **11, 14, 16, 18, 19, 21-25,** and **58** are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for *a method of treating Alzheimer's disease in a mammalian subject, comprising administering to the subject a dosage of $A\beta_{42}$ (AN1792) effective to produce an immune response comprising antibodies against said of $A\beta_{42}$ (AN1792) and an adjuvant that augments the immune response to said $A\beta_{42}$ (AN1792)*, does not reasonably provide enablement for *prevention of a hereditary Alzheimer's disease, Down's syndrome, hereditary cerebral hemorrhage (Dutch type), sporadic cerebral amyloid angiopathy or inclusion body myositis or treatment of Down's syndrome, hereditary cerebral hemorrhage (Dutch type), sporadic cerebral amyloid angiopathy or inclusion body myositis in a mammalian subject using said method or use of other agents*. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims for the reasons as set forth in at pp. 5-11 ¶11-23 of the previous Office Action (Paper No. 10, 27 November 2002).

14. The Applicant traverses the 35 U.S.C. §112 ¶1 rejection of claims **11, 14, 16, 18, 19,** and **20-25** as set forth in at pp. 5-11 ¶12-23 of the previous Office Action (Paper No. 10, 27 November 2002) now including claim **58** on the following grounds: **(a)** the PDAPP mouse model is a good mouse model for Alzheimer's disease, **(b)** Declaration under 35 C.F.R. §1.132 of Martine Koller, M.D., M.P.H. (Paper No. 16 filed 28 May 2003), **(c)** adequate guidance is presented to practice the invention, **(d)** no undue experimentation is required to evaluate all of the cellular and humoral effects of $A\beta_{42}$ (AN1792) fragments to practice in the invention, **(e)** citing *In re Brana* (Fed. Cir. 1995) the Applicant argues that the USPTO is not responsible for

testing therapies, **(f)** the mutations claimed are known in the art, **(g)** Tanaka's study was done without adjuvant, and **(h)** a nexus between active and passive immunization and therapeutic effects is present for Alzheimer's disease. Applicant's arguments have been fully considered but are not deemed to be persuasive for the following reasons.

15. The instant claims are drawn very broadly to a method of preventing or treating amyloid diseases and disorders via active immunization with an agent, for example, $A\beta_{42}$ (AN1792). The language of said claims encompasses both *treatment* and *prevention* amyloid disorders which covers a broad range of disorders {see Sipe (1992) "Amyloidosis." Annu. Rev. Biochem. **61**: 947-975 and Tan & Pepys (1994) "Amyloidosis." Histopathology **25**: 403-414}. It is noted that "Prevention" is understood to mean the complete and total stoppage of any Alzheimer's disease signs and symptoms. Thus it is an "all-or-nothing" effect, not a lowered incidence of disease or an alleviation of symptoms.

16. The specification teaches that the administration of particular $A\beta_{42}$ (AN1792) fragments with an immunogenic adjuvant reduces β-amyloid levels within the brains of transgenic PDAPP mice. These mice exhibit Alzheimer's disease type over production and build up of β-amyloid within the brain {Chapman (21/28 December 2000) "Model Behavior." Nature **408**: 915-916}.

17. Since the specification fails to provide any guidance for the successful prevention of amyloid disorders via active immunization, and since resolution of the various complications in regards to treating amyloid disorders and disorders is highly unpredictable, one of skill in the art would have been unable to practice the invention without engaging in undue trial and error experimentation. In order to practice the invention using the specification and the state of the art as outlined below, the quantity of experimentation required to practice the invention as claimed

would require the *de novo* determination of formulations with known amyloid proteins, amyloidosis signs and symptoms to correlate with prevention of said amyloidosis. In the absence of any guidance from the specification, the amount of experimentation would be undue, and one would have been unable to practice the invention over the scope claimed.

18. The specification as filed does not provide any guidance or examples that would enable a skilled artisan to use the disclosed method of using $A\beta_{42}$ (AN1792) fragments for active immunization in a patient to prevent an amyloid disorder. Thus, although the specification prophetically considers and discloses general methodologies of using the claimed method for prevention, such a disclosure would not be considered enabling since the state of amyloidosis is highly unpredictable. The factors listed below have been considered in the analysis of enablement:

(A) The breadth of the claims;
(B) The nature of the invention;
(C) The state of the prior art;
(D) The level of one of ordinary skill;
(E) The level of predictability in the art;
(F) The amount of direction provided by the inventor;
(G) The existence of working examples; and
(H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

19. On "**(a)**", the Examiner *accepts* the Applicant's argument that the PDAPP mouse is a representative mouse model of Alzheimer's disease {see Chapman (21/28 December 2000) "Model Behavior." Nature **408**: 915-916}. However, the instant claims, as amended, are directed to prevention of a wide range of diseases and disorders which involve amyloid deposition of Aβ deposits. While being enabled for using active immunization of $A\beta_{42}$ (AN1792) fragments to

treat Alzheimer's disease, the Specification does not provide sufficient support for the great range of amyloidosis diseases and disorders encompassed by the instant claims.

20. In response to "**(b)**", the Declaration of Martine Koller, M.D., M.P.H. under 37 CFR §1.132 filed 28 May 2003 (Paper No. 16), is insufficient to overcome the rejection of claims 11, 14, 16, 18, 19, and 21-25 based upon lack of enablement under 35 U.S.C. §112 ¶1 as set forth in the last Office action because: the evidence provided in said Declaration is not commensurate in scope with the instant claims. Said Declaration does not demonstrate prevention of Alzheimer's disease or provide evidence that the claimed method would have any effect on Down's syndrome, hereditary cerebral hemorrhage (Dutch type), sporadic cerebral amyloid angiopathy or inclusion body myositis or treatment of Down's syndrome, hereditary cerebral hemorrhage (Dutch type), sporadic cerebral amyloid angiopathy or inclusion body myositis. In light of the breadth of the claims, "Prevention" is understood in the art to mean a total protection from disease or injury. Thus, given the high level of required effect, a high level of evidence showing prevention is also required. While the specification demonstrates a level of relief from symptoms of using $A\beta_{42}$ (AN1792) fragments as an immunogen in mice and humans, total prevention was not achieved.

21. In response to "**(c)**", the Examiner *accepts* the Applicant's argument to the extent that the Specification provides ample evidence to use active immunization of $A\beta_{42}$ (AN1792) fragments to treat Alzheimer's disease in mammalian subjects (those suffering from Alzheimer's disease).

22. Concerning "**(d)**", the Examiner *accepts* the Applicant's argument to the extent that the Specification provides ample evidence to use active immunization of $A\beta_{42}$ (AN1792) fragments to treat Alzheimer's disease in mammalian subjects (those suffering from Alzheimer's disease).

23. To address "**(e)**", the Examiner *accepts* the Applicant's argument that the USPTO is not responsible for testing the effectiveness of active immunization of $A\beta_{42}$ (AN1792) fragments. The Examiner reiterates the that the Specification provides ample evidence to use active immunization of $A\beta_{42}$ (AN1792) fragments to treat Alzheimer's disease in mammalian subjects (those suffering from Alzheimer's disease). Thus even when faced with possible inflammatory side effects, the claimed method may provide relief from Alzheimer's disease. The Examiner *accepts* the Applicant's argument that a clinician ("one skilled in the art") would be able to accommodate for such side effects and practice the claimed method of using active immunization of $A\beta_{42}$ (AN1792) fragments to treat Alzheimer's disease with an on balance, positive therapeutic effect.

24. In response to "**(f)**", the Examiner *maintains* that only the $A\beta_{42}$ AN1792 fragment for active immunization and not all fragments thereof. The skilled artisan readily recognizes that protein chemistry is an unpredictable area of biotechnology. Proteins with deletion, insertion or substitution/replacement of single amino acid residues may lead to both structural and functional changes in biological activity and immunological recognition, see in particular Skolnick & Fetrow (2000) "From genes to protein structure and function: novel applications of computational approaches in the genomic era." Trends in Biotech. **18**(1): 34-39 (**IDS #337**). For example, Jobling & Holmes (1991) "Analysis of structure and function of the B Subunit of cholera toxin by the use of site-directed mutagenesis." Molecular Microbiology **5**(7): 1755-67

(**IDS #334**) teaches a panel of single amino acid substitutions by oligonucleotide directed mutagenesis which produce proteins that differ in native conformation, immunological recognition, binding and toxicity. The skilled artisan further recognizes that immunological responses may depend upon the structural characteristics (conformation) of the particular protein (amino acid sequence) targeted. Thus, both biological function and immunological recognition are unpredictable properties which must be experimentally determined. Further it is noted, that for particularly small peptides, conjugation appears to be required for promoting an effective immune response. Thus the skilled artisan is not presented with sufficient guidance in the instant Specification to practice the invention to the full scope of use of all as of yet unspecified fragments of Aβ.

25. The issue in "**(g)**" is *moot* in view of Applicant's current amendment of claim 11.

26. The issue in "**(h)**" the Examiner *accepts* the Applicant's argument to the extent that the Specification provides ample evidence to use active immunization of $A\beta_{42}$ (AN1792) fragments to treat Alzheimer's disease in mammalian subjects (those suffering from Alzheimer's disease).

27. The rejection of claims **11, 14, 16, 18, 19, 21-25,** and **58** under 35 U.S.C. §112 ¶1 is maintained.

28. The rejection of claims **11, 14, 16, 18, 19, 21-25,** and **58** under provisional obvious-type non-statutory double patenting as set forth at pp. 11-14 ¶22-29 in the previous Office Action (Paper No. 10, 27 November 2002) is *maintained.*

Summary

29. No claims are allowed.

30. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Christopher James Nichols, Ph.D.** whose telephone number is 703-305-3955. The examiner can normally be reached on Monday through Friday, 8:00AM to 5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Gary Kunz, Ph.D.** can be reached on 703-308-4623. The fax phone numbers for the organization where this application or proceeding is assigned are 703-872-9306 for regular communications and 703-872-9307 for After Final communications. The fax phone numbers for the customer service center is 703-872-9305

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Elizabeth C. Kemmerer

CJN
July 11, 2003

ELIZABETH KEMMERER
PRIMARY EXAMINER